Demystifying Medicine 2019

Cellular Immunotherapy of Cancer

CAR-T Cell Therapy in Pediatric Leukemia

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Tuesday, February 26, 2019

Disclosures

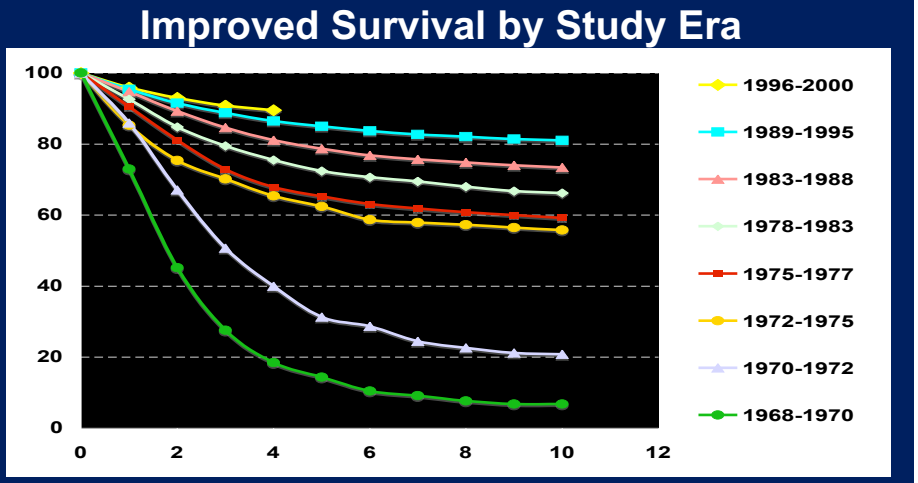
- No disclosures to report
- I will be discussing utilization of novel (non-FDA approved) CAR-T cell approaches in pediatric leukemia

Educational Objectives

- Provide a general overview of CAR-T Cell therapy in pediatric acute lymphoblastic leukemia (ALL)
- Discuss future directions and challenges in immunotherapy for ALL

Childhood Acute Lymphoblastic Leukemia (ALL)

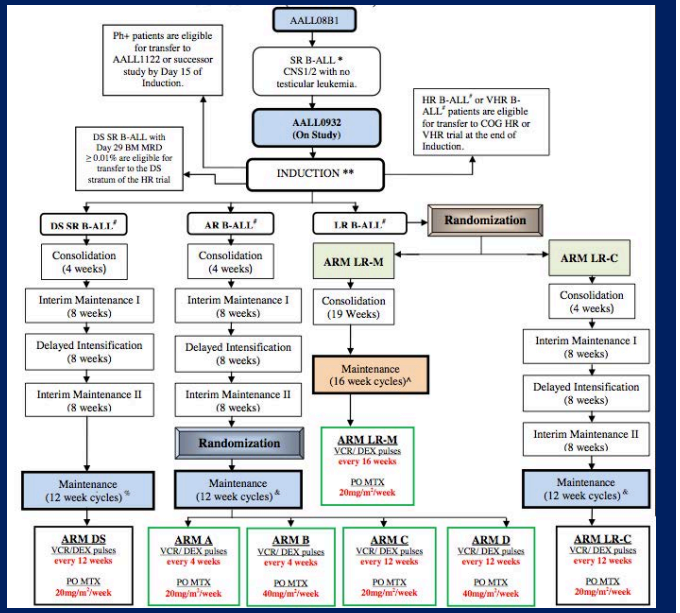
- Most common cancer diagnosed in children.
  - 41 cases/million in children aged < 14
  - 17 cases/million in teens between ages 15-19
  - 25% of all new cancer diagnosis
- 85-90% of patients will be cured.
- "Poster-child" for efficacy and importance of cooperative groups and clinical trial participation.

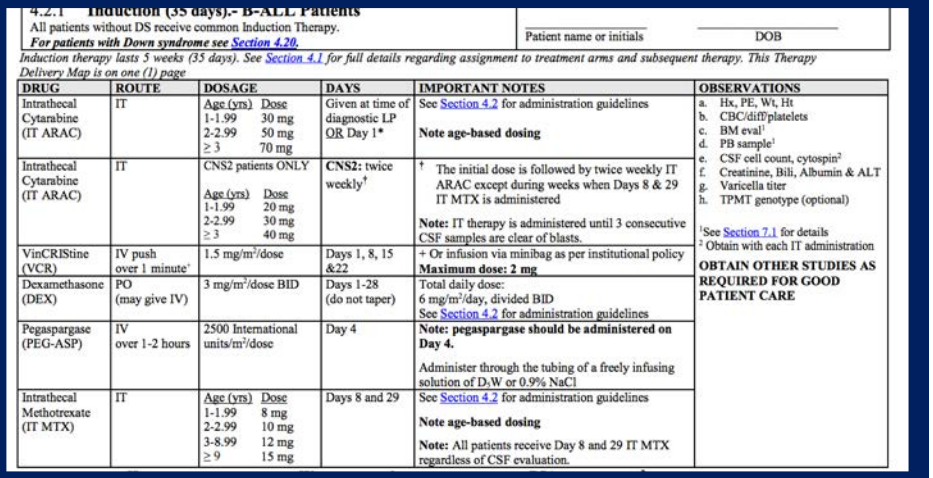


Data courtesy of GH Reaman, H Sather, Children's Oncology Group

Current Treatment Plan

- Combinatorial chemotherapy treatment strategy with non-competing mechanisms of action.
- Series of intensified/de-intensified treatment cycles.
- Prolonged maintenance phase (2-3 years)
- Risk-adapted approach





4.2.1 Induction (35 days).- B-ALL Patients

All patients without DS receive common Induction Therapy.

For patients with Down syndrome see Section 4.20.

Patient name or initials _____ DOB _____

Induction therapy lasts 5 weeks (35 days). See Section 4.1 for full details regarding assignment to treatment arms and subsequent therapy. This Therapy Delivery Map is on one (1) page

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Cytarabine (IT ARAC)	IT	Age (yrs) Dose 1-1.99 30 mg 2-2.99 50 mg ≥ 3 70 mg	Given at time of diagnostic LP OR Day 1*	See Section 4.2 for administration guidelines **Note age-based dosing**	a. Hx, PE, Wt, Ht b. CBC/diff[1]/platelets c. BM eval[1] d. PB sample[1] e. CSF cell count, cytospin[2] f. Creatinine, Bili, Albumin & ALT g. Varicella titer h. TPMT genotype (optional) [1]See Section 7.1 for details [2] Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intrathecal Cytarabine (IT ARAC)	IT	CNS2 patients ONLY Age (yrs) Dose 1-1.99 20 mg 2-2.99 30 mg ≥ 3 40 mg	**CNS2:** twice weekly†	† The initial dose is followed by twice weekly IT ARAC except during weeks when Days 8 & 29 IT MTX is administered **Note:** IT therapy is administered until 3 consecutive CSF samples are clear of blasts.	
VinCRIStine (VCR)	IV push over 1 minute^	1.5 mg/m²/dose	Days 1, 8, 15 &22	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Dexamethasone (DEX)	PO (may give IV)	3 mg/m²/dose BID	Days 1-28 (do not taper)	Total daily dose: 6 mg/m²/day, divided BID See Section 4.2 for administration guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Day 4	**Note: pegaspargase should be administered on Day 4.** Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 8 and 29	See Section 4.2 for administration guidelines **Note age-based dosing** **Note:** All patients receive Day 8 and 29 IT MTX regardless of CSF evaluation.	

Outcomes for Relapsed/Refractory Disease

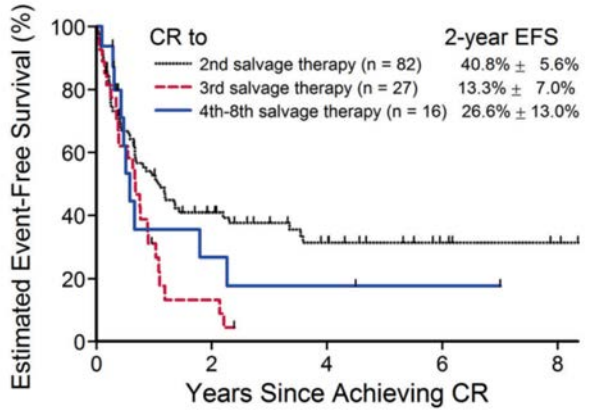


Fig. 2 Estimated 2 year event-free survival for patients who achieved complete remission after ≥2nd salvage attempt. CR complete remission, EFS event-free survival

Table 4 Comparison of unadjusted CR rates of patients with medullary relapsed/refractory ALL between two sequential TACL studies

Number of salvage attempt	CR rate (SE) [95% confidence interval]		Difference (Sun–Ko) (SE) (testing proportion)
	1995–2004 (Ko et al.) [5]	2005–2013 (Sun et al.)	
Second salvage attempt	44.44 % (4.78) [34.88, 54.32]	50.91 % (3.89) [43.02, 58.76]	0.0647 (0.0616) (−0.0561, 0.1855) $p = 0.2955$
Third salvage attempt	26.78 % (5.92) [15.83, 40.30]	36.99 % (5.65) [25.97, 49.09]	0.1021 (0.0818) (−0.0583, 0.2624) $p = 0.2200$
Fourth through eighth salvage attempt	12.31 % (4.07) [5.47, 22.82]	30.77 % (6.40) [18.72, 45.10]	0.1846 (0.0759) (0.0358, 0.3333) $p = 0.0140$

CR complete remission, *SE* standard error

Sun/Whitlock, Leukemia, 2018

Challenges

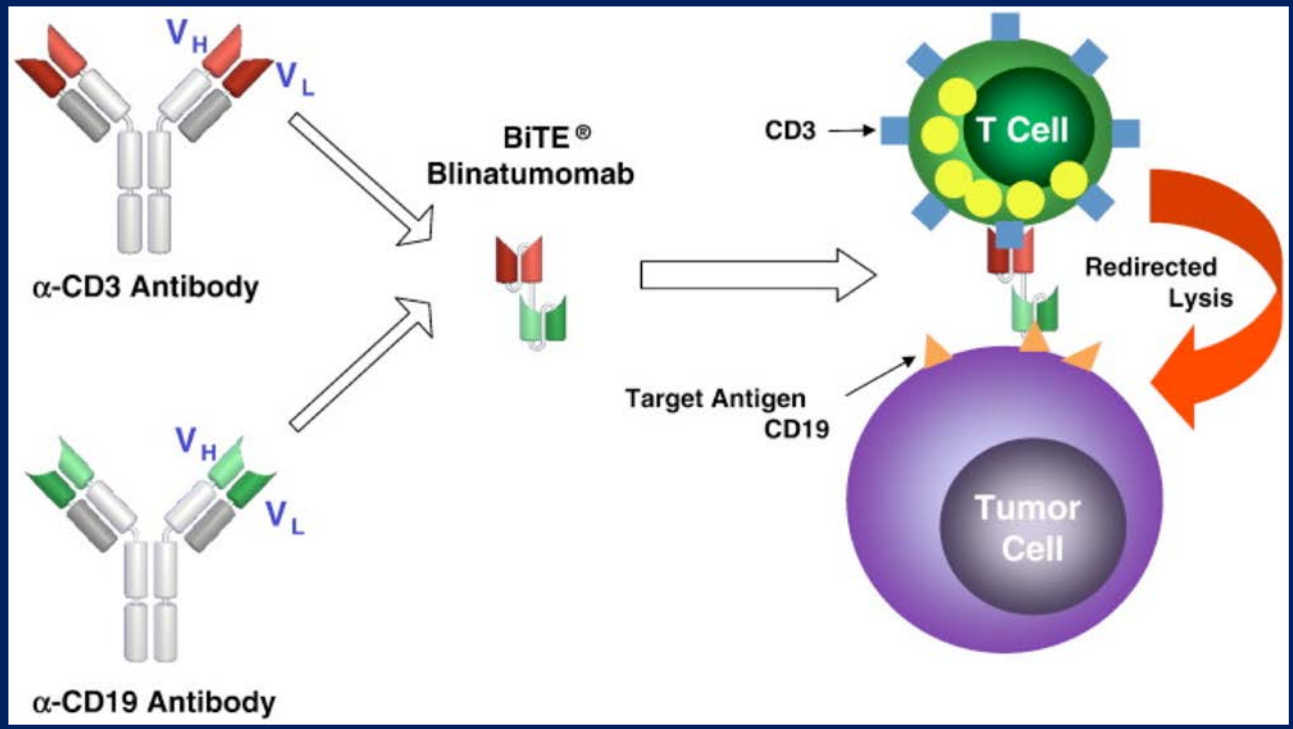
- Curative options for relapsed/refractory disease remains a therapeutic challenge
- Outcomes for the adolescent young adult (AYA) population remain particularly poor
- Toxicity from cumulative therapy not insignificant
- Novel therapies are needed

Lets meet our special guest…

Treatment Overview

- Diagnosis: May 2016, standard risk→ but with poor response at day 8
- Transitioned to high-risk treatment arm, but with relapse during maintenance (October 2017)
- Started re-induction chemotherapy and randomized to receiving blinatumomab (anti-CD19/CD3 targeted therapy)
  - Transient incomplete response
- Referred to CD19 CAR T cell therapy (April 2018)
- Achieved remission but relapsed July 2018

Blinatumomab

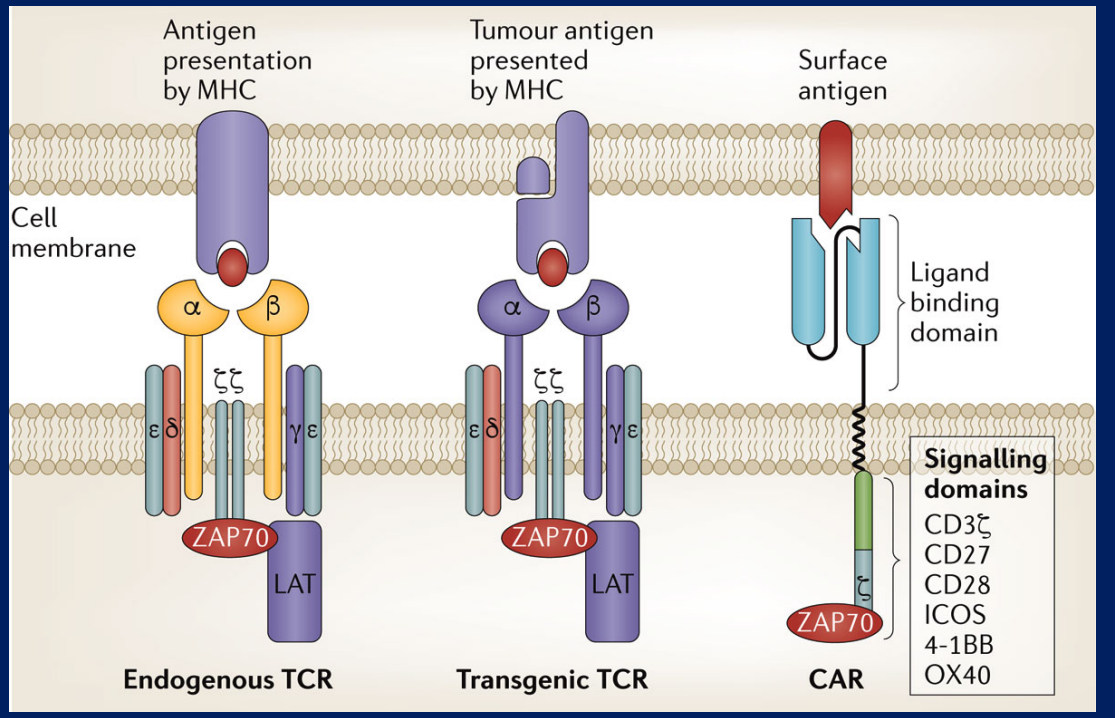


- 50-70% CR rate in adults
- 30-40% CR rate in children

TCRs and CARs

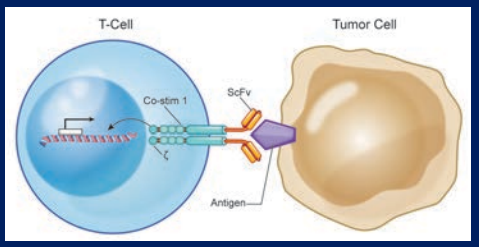
- TCR: T-cell receptor
  - Recognize processed antigens and are MHC dependent, and require co-stimulatory signals for T-cell activation
- CAR-T cell: chimeric antigen receptor T-cell
  - Recognize cell surface antigens independent of MHC, have co-stimulatory signals integrated
  - Retains the functionality of a T-cell with the antigen recognition properties of antibody

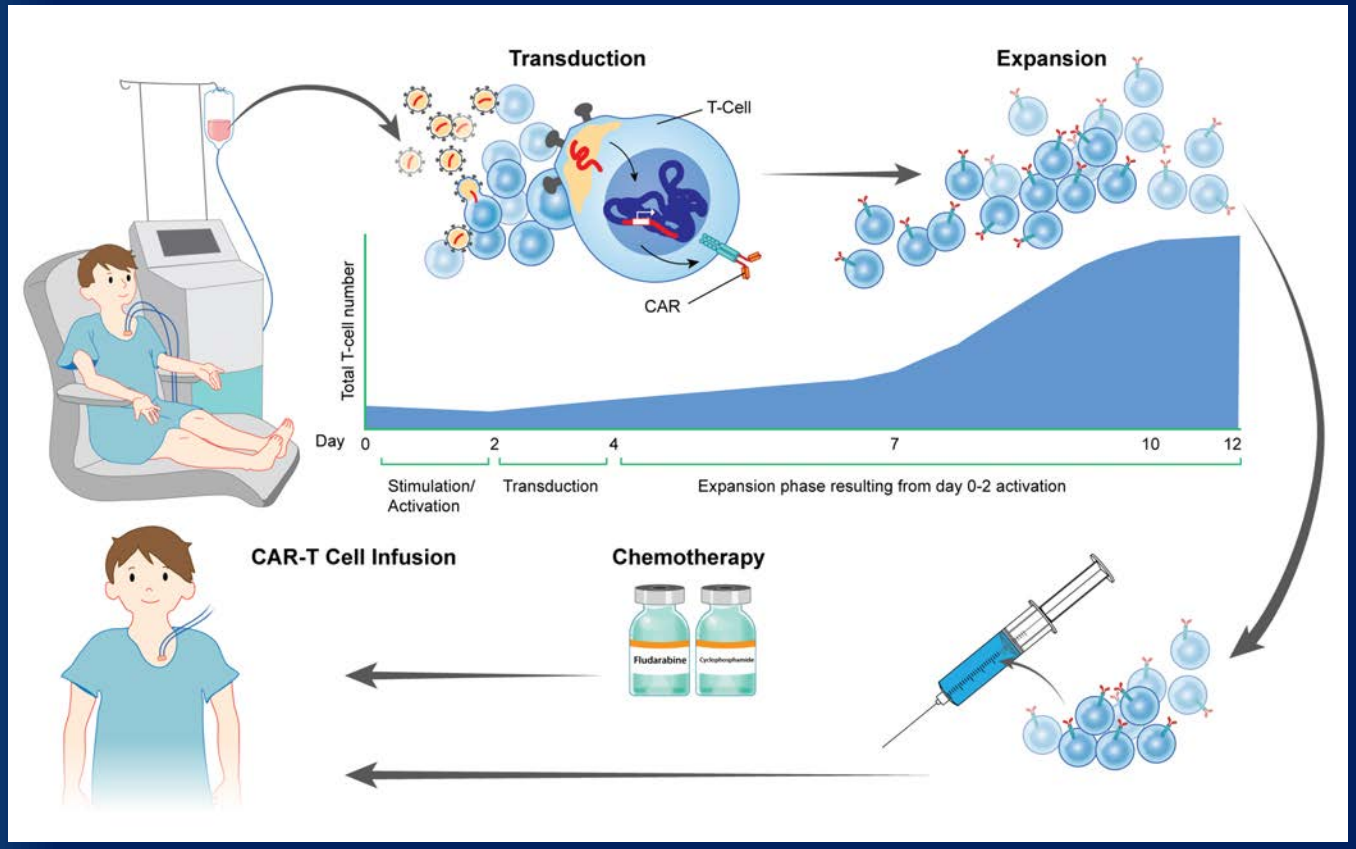
TCR vs CAR-T Cell Structure



Fesnak et al. Nature Review Clin. Oncology, 2016

Making a CAR-T Cell





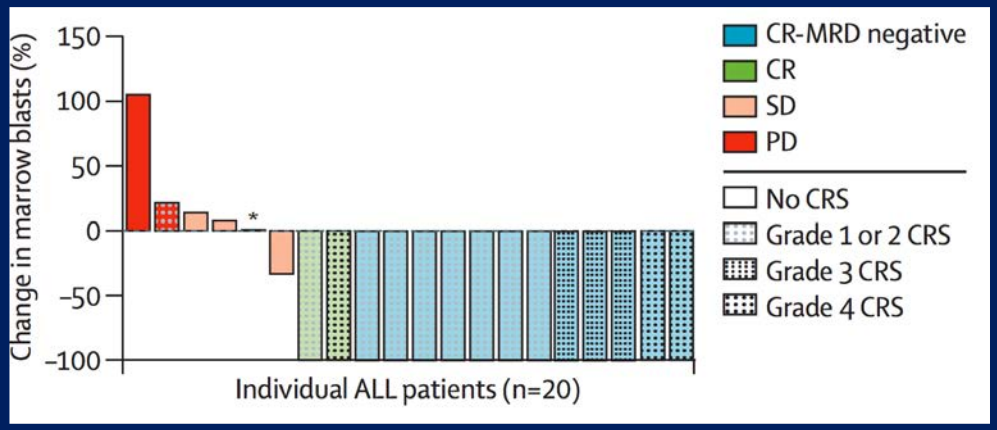
1. Apheresis
2. Stimulation and Transduction
3. Expansion
4. Lymphodepletion
5. Infusion

Image, Courtesy of NIH Medical Arts

CD19 CAR Clinical Updates (NCI-POB)

T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial

Daniel W Lee, James N Kochenderfer, Maryalice Stetler-Stevenson, Yongzhi K Cui, Cindy Delbrook, Steven A Feldman, Terry J Fry, Rimas Orentas, Marianna Sabatino, Nirali N Shah, Seth M Steinberg, Dave Stroncek, Nick Tschernia, Constance Yuan, Hua Zhang, Ling Zhang, Steven A Rosenberg, Alan S Wayne, Crystal L Mackall



Lee et al. Lancet 2015
67% CR rate (ITT)
All responders with CRS

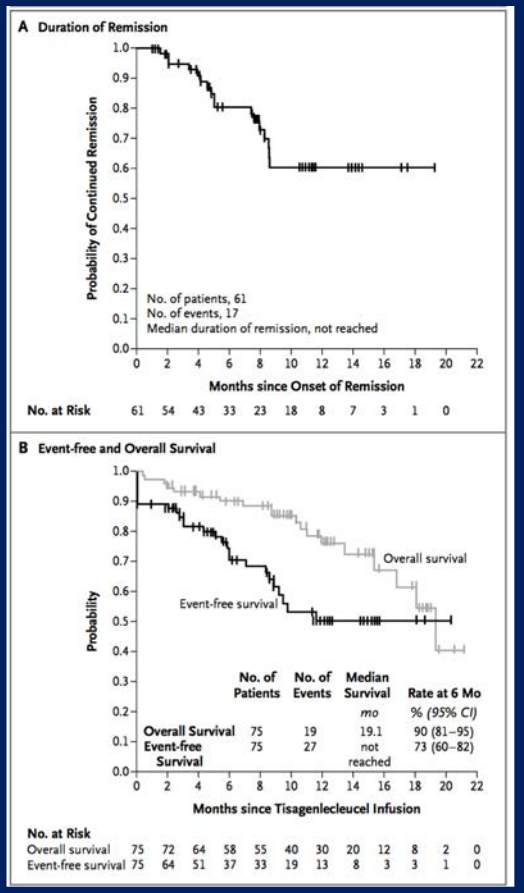
CD19 CAR Clinical Updates (Novartis)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

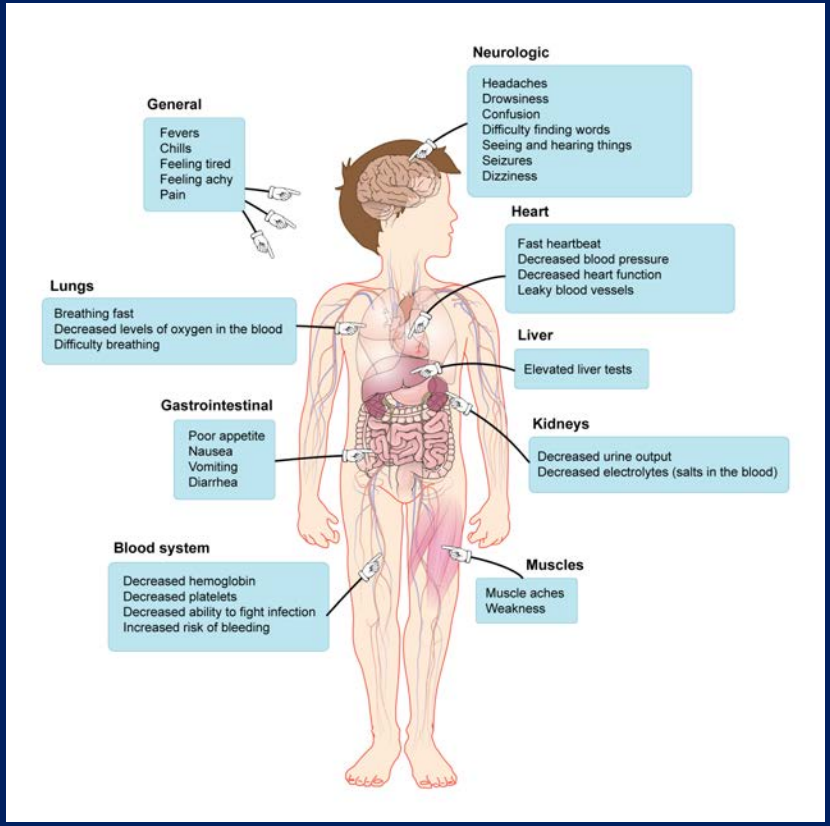
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

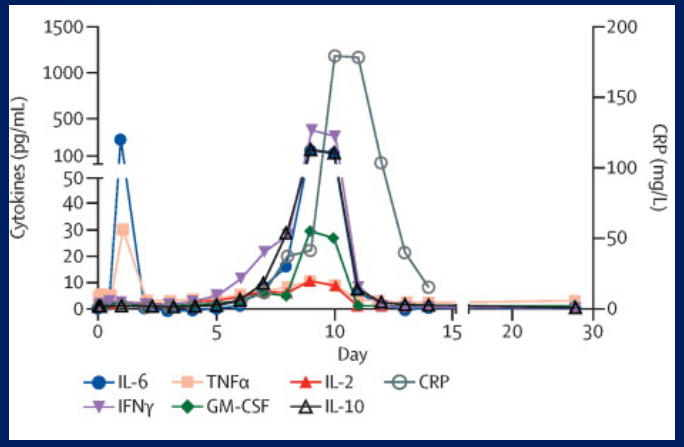
S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

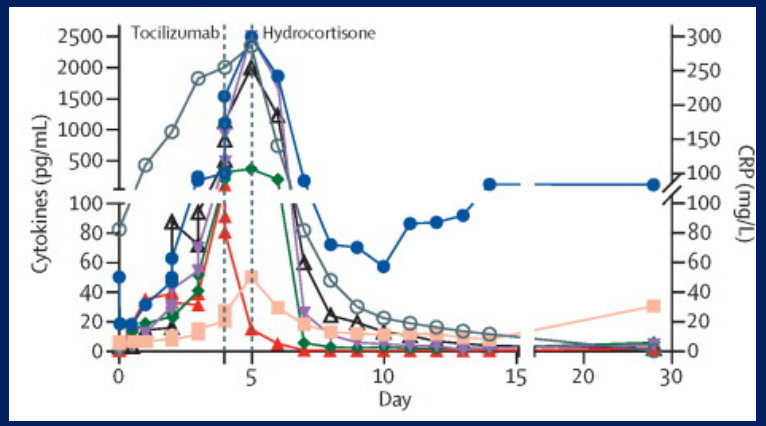


81% Complete remission rate (not ITT)

Cytokine Release Syndrome





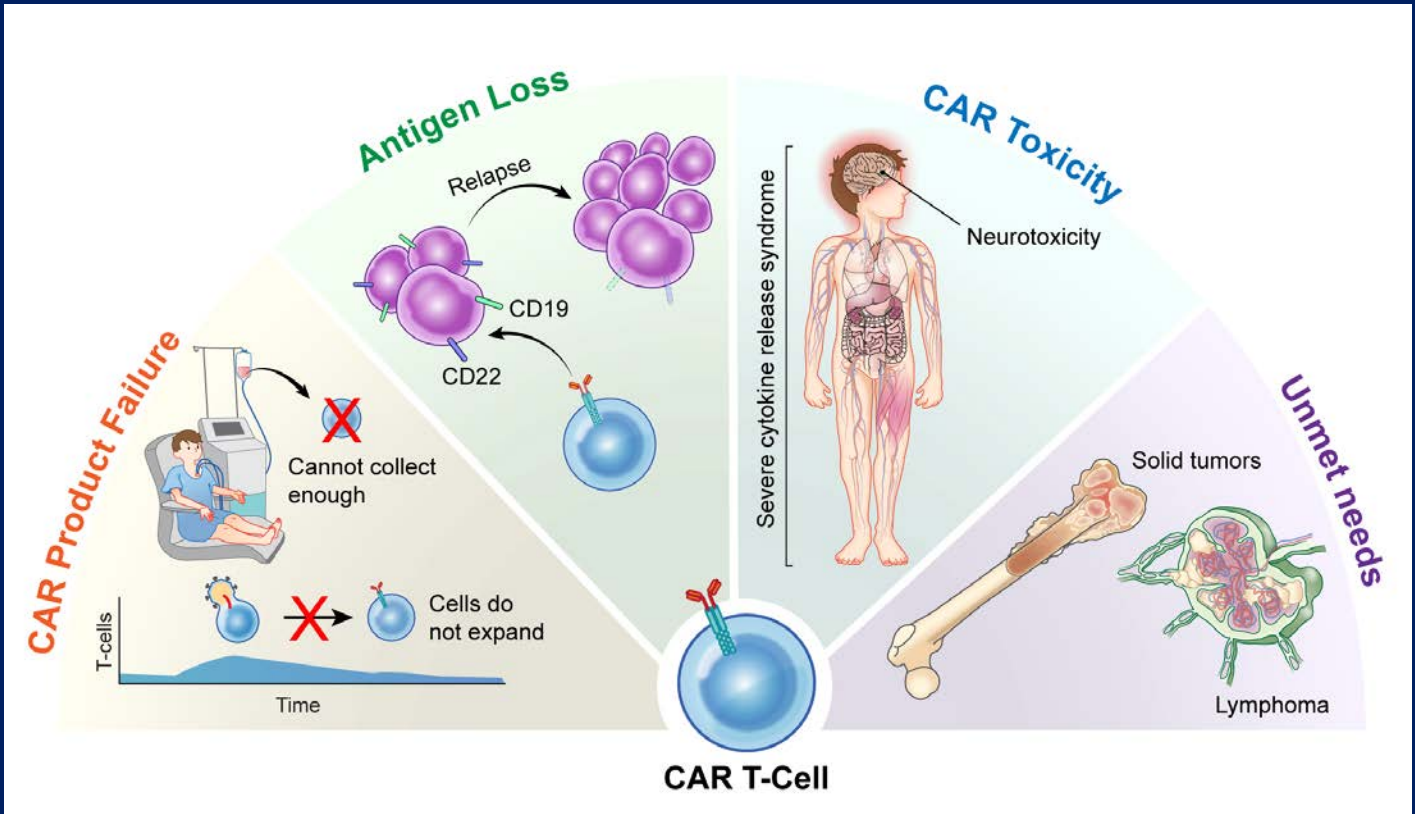


Images, Courtesy of NIH Mediccal Arts
Lee/Mackall Lancet 2015

CAR Therapies: FDA Approval

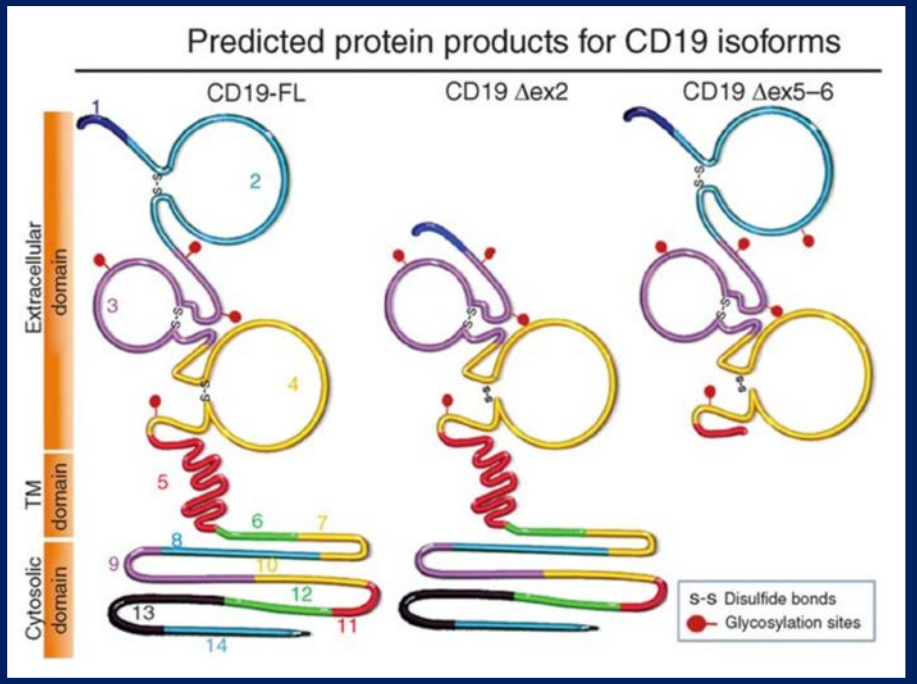
- Kymriah™ (tisagenlecleucel, Novartis): For children up to age 25 with ALL (August 2017)
- Tocilizumab: To treat CAR T-cell related CRS (August 2017)
- Yescarta™ (axicabtagene ciloleucel, KITE): For adults with Diffuse Large B Cell Lymphoma (October 2017)
- **Complete remission rates: +/- 50-80%**

Limitations to Durable Remissions



Oh Where… Oh Where… Has my CD19 gone?

- At least ONE identified mechanism:
  - Loss of the surface epitope, but retention of the target protein (in part)
  - Due to clustering of nonsense and missense mutations in exon 2 of CD19
  - Specific frameshift mutation eliminates full-length CD19 but allows expression of an isoform
    - Mostly cytosolic and hidden from T cells
  - Hallmark of relapsed leukemia post CAR was lack of the full-length isoform



Sotillo/Thomas-Tikhonenko, Cancer Discovery 2015

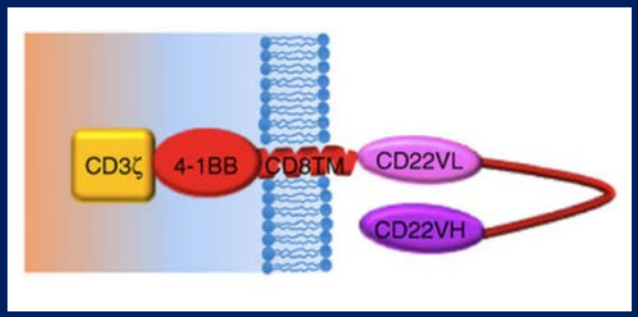
Lineage Switch (ALL→ AML)

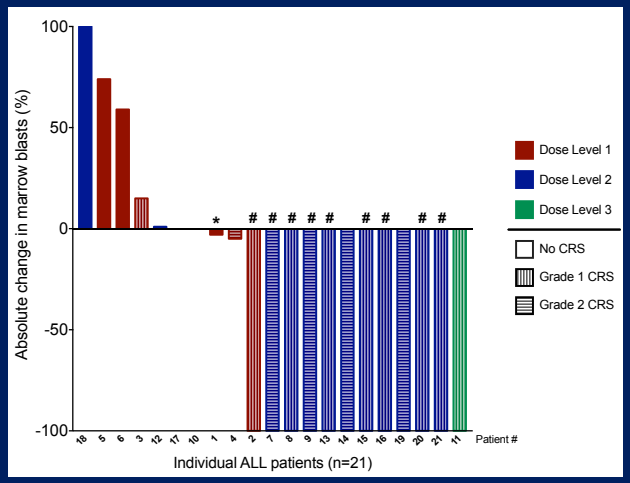
- *MLL*-rearranged B-ALL (11q23) rearrangement
  - "Infant" ALL→ VERY poor prognosis
- Gardner et al.
  - 7 of 7 with *MLLr*-ALL attained MRD neg CR post –CD19 CAR
  - Relapses seen in 2 with myeloid phenotype
- Similar experience seen in *MLLr*-ALL treated with blinatumomab
- Jacoby et al.
  - CD19 CAR immune pressure induces lineage switch

Gardner/Turtle, Blood 2015
O'Brien, Pediatric Blood Cancer 2016
Jacoby/Fry Nat Commun 2016

Phase I Study of Anti-CD22 CAR

- Novel CAR construct targeting CD22
- Heavily pre-treated population
- CRS was less severe (Grades 1 and 2)
- Limited neurotoxicity
- Unique toxicities:
  - Capillary leak
  - Coagulopathy
  - Hemolytic uremic syndrome

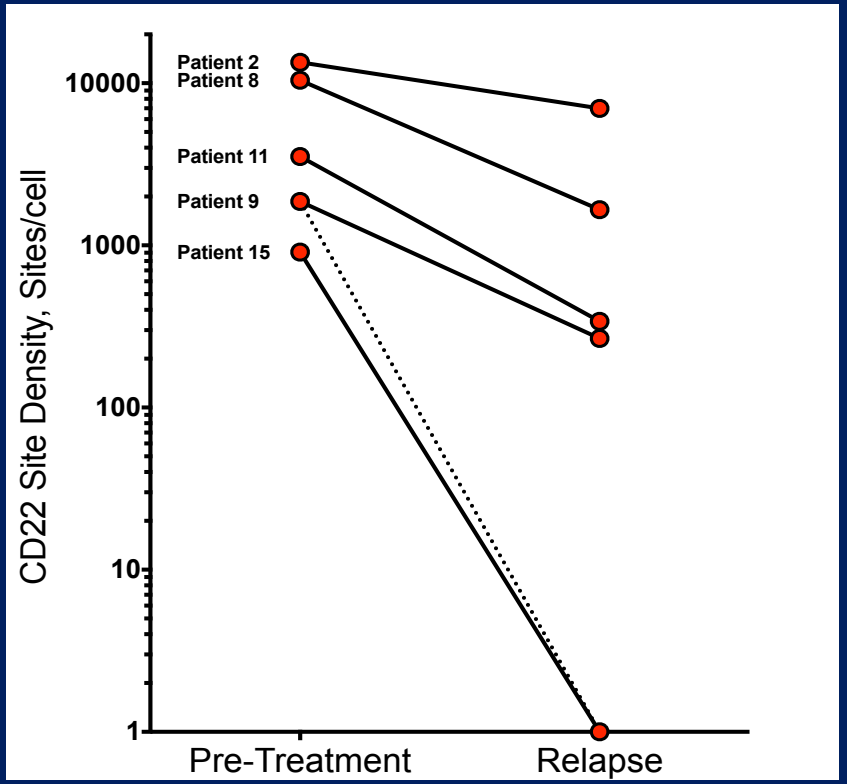




Fry TJ, Nat. Medicine 2018

CD22 Antigen Expression at Relapse

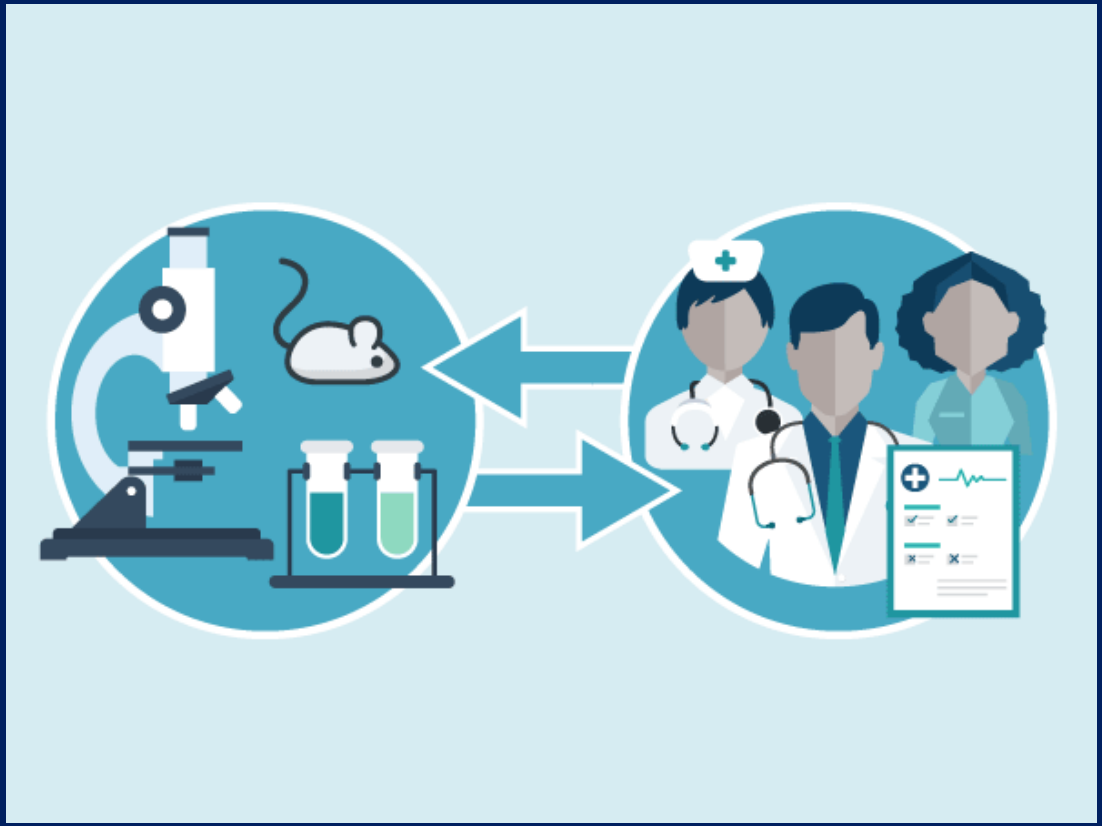
- Decrease in Site Density
- Antigen loss
- Both
- No genomic mutation, modulation of gene expression or altered isoform expression was found in patients with relapse (limited samples)



Treatment Overview

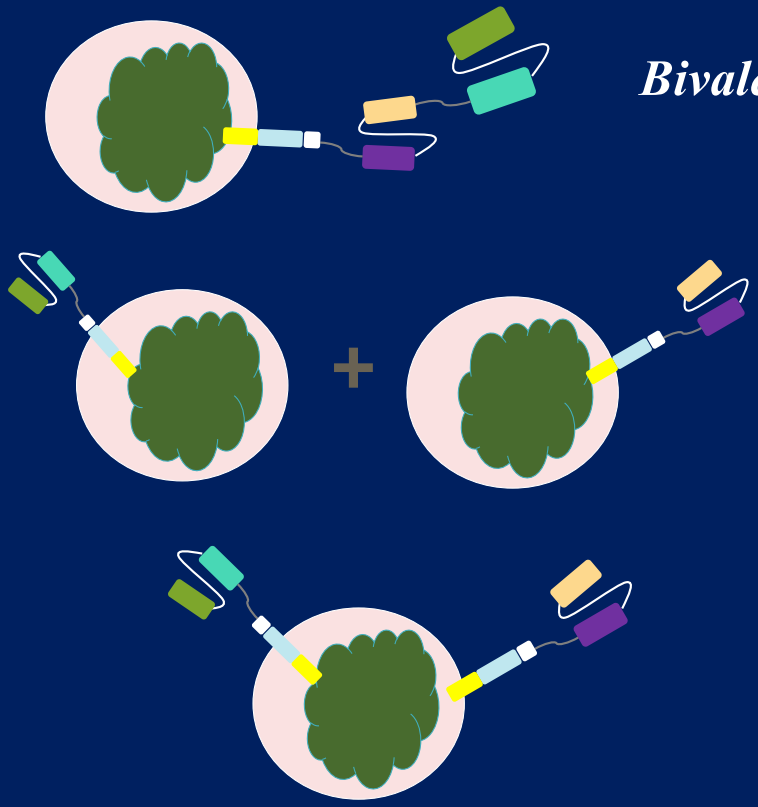
- Treated on CD22 CAR T cells
- Achieved remission
- Proceeded to Bone marrow transplant

Bench to Bedside to Bench



Our Patients Inspire Change

Options for Simultaneous Targeting of CD19 and CD22 (Fry Lab)



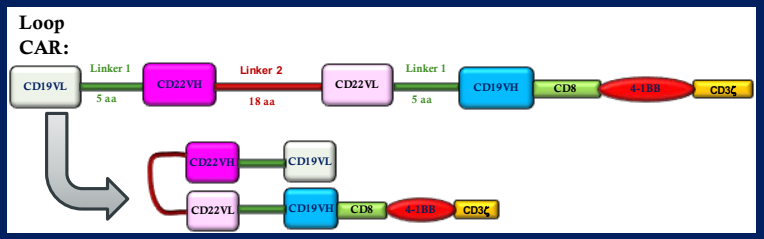
Bivalent-Bispecific Receptor

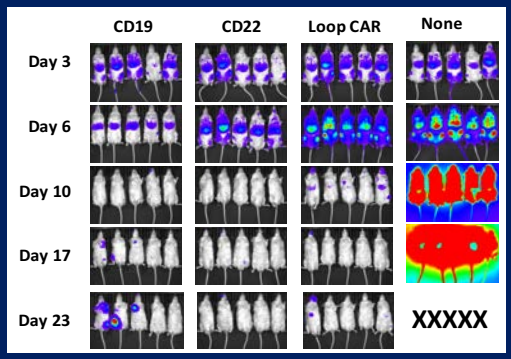
Co-administration

Co-expression

Phase 1 Dose Escalation Study of Anti-CD19/CD22 Chimeric Antigen Receptor (CAR) T Cells in Children and Young Adults with Recurrent or Refractory CD19/CD22-expressing B Cell Malignancies

- Hypothesis: Simultaneous targeting of CD19 and CD22 could diminish the risk of antigen loss escape
- Novel bivalent, bispecific CAR to be tested in the clinic
- Actively enrolling





Activity of Bispecific CAR:
***In vivo* activity against CD19+/22+ B-ALL**

Qin et. al. Molecular Therapy Oncolytics

Future Directions

- Novel CAR constructs:
  - AML CAR
  - Bi-specific CAR
- Optimizing second infusions
- Improving CAR persistence
- Increasing tumor sensitivity by enhancing antigen expression
- Bringing CAR constructs earlier into the therapeutic plan
- Exploring response in lymphoma and CNS disease
- Decreasing toxicity
- Improving access to therapy

Acknowledgements

- Terry J. Fry
- Brigitte Widemann
- John Glod
- Haneen Shalabi
- Bonnie Yates
- Cindy Delbrook
- Maryalice Stetler-Stevenson
- Constance Yuan
- Leah Hoffman
- Pamela Wolters
- Crystal L. Mackall
- Daniel "Trey" Lee
- Rimas Orentas
- Steve Highfill
- David Stroncek
- Haiying Qin
- Naoza Collins-Johnson
- Staci Martin
- Lori Wiener
- Sima Zadeh
- Joan Galil
- Kamille West
  Cathy Cantilena
- Paul Jarosinski
- Nursing

A special thanks to all our patients, particularly those who are no longer with us, their families and referring teams. Their memory lives on in our work.